Original Research

AMERICAN ACADEMY OF OTOLARYNGOLOGY–HEAD AND NECK SURGERY FOUNDATION

OTO Open
2020, 4(4) 1–7

DOI: 10.1177/2473974X20978133
http://oto-open.org
SAGE

Temporal Profile of Olfactory Dysfunction in COVID-19

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Abstract

Objective. Coronavirus disease 2019 (COVID-19) is associated with olfactory dysfunction, but the evolution of the olfactory loss and timeline to recovery are largely unknown. This study examines changes in smell sensitivity in COVID-19–positive (COVID+) and COVID-19–negative (COVID–) viral illness during the initial weeks after infection.

Study Design. Cross-sectional cohort comparison.

Setting. National anonymous surveys.

Methods. Survey participants were queried about smell sensitivity and general health status at the time of COVID-19 testing and in the weeks that followed.

Results. In total, 375 (174 COVID+, 201 COVID–) participants completed the survey and 132 (62 COVID+, 70 COVID–) participants completed the 2-week follow-up survey. Normal smell in the COVID+ cohort was less frequent at the time of testing and at follow up ($P < .05$). Dynamic changes in smell sensitivity in the COVID+ cohort were more frequent in the initial weeks ($P < .001$). In those with normosmia at the start of infection, 38% of the COVID+ cohort reported worsening smell compared to only 8% in the COVID– cohort ($P < .05$). Recovery of overall health was associated with normosmia at the time of infection and improvement of smell sensitivity within weeks of infection.

Conclusion. The COVID+ cohort showed greater dynamic change in smell sensitivity and a higher rate of persistent olfactory dysfunction in the weeks after infection. Normal smell at the time of COVID-19 infection may still worsen before recovery. Overall health recovery after viral illness is associated with improvement in smell sensitivity and the absence of initial anosmia or hyposmia.

Keywords

smell, olfaction, recovery, COVID-19

Received September 10, 2020; accepted November 11, 2020.

Olfactory dysfunction is common, with a prevalence of 12.4% (13.3 million adults in the United States) found in the 2012 National Health and Nutrition Examination Survey (NHANES) database based upon objective smell testing.[1] Smell loss has significant impact on quality of life and can lead to depression from a lack of enjoyment in life, safety concerns (gas leak, fires, spoiled food), and malnutrition.[2-4] The most common causes of olfactory dysfunction include nasal and sinus disorders, upper respiratory tract infections (URTIs), age, head trauma, smoking, and neurodegenerative diseases.[5]

Acute decline in olfactory function from URTIs may be caused by either nasal congestion and obstruction or direct injury to the neurosensory cells required for olfaction. When concurrent nasal congestion creates a conductive pattern of olfactory loss, olfaction frequently recovers as the viral illness and its accompanying symptoms resolve. However, if a neurosensory insult to the olfactory cells has occurred, the olfactory dysfunction can persist following resolution of the URTI and is defined as postviral olfactory dysfunction (PVOD).[6] PVOD may take months or years to recover and, in some cases, becomes permanent.[7] PVOD is more common in women and during the fourth to eighth decades of life.[6] The level of smell recovery has been associated with age, degree of initial smell loss, and duration of the smell loss.[8]

The actual incidence of acute olfactory dysfunction during and following a viral infection is largely unknown, likely due to the fact that patients do not report mild smell impairment when URTI symptoms dominate and do not seek medical care for PVOD until long after the acute URTI has resolved.[9] The most common physiologic cause of olfactory dysfunction related to an acute URTI is the presence of mucosal edema and inflammation that obstruct

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odorants from reaching the olfactory cleft.[9] However, when smell impairment persists after resolution of nasal inflammation, then direct damage to peripheral olfactory receptor cells is suspected. In an electron microscopy study, olfactory mucosa biopsies from postviral anosmics demonstrate a reduced number of intact ciliated olfactory receptor neurons.[10] In addition to a peripheral olfactory insult, a central mechanism is also possible, such as functional reorganization of the piriform cortex, which integrates sensory odorant input with higher cortical information.[7,11]

Smell and taste loss have more recently been associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID+),[12] with up to 70% of affected patients reporting chemosensory changes.[13,14] Similar to resolution of olfactory dysfunction that occurs with the common cold, recovery of COVID+ olfactory loss has generally been associated with recovery from other disease-related symptoms. The timing of olfactory function recovery was reported to occur less than 2 weeks after diagnosis in 1 study[15] and within 3 weeks (median time 7 days) in another study.[16] Information on recovery of olfactory loss from COVID-19 compared to non–COVID-19 (COVID–) URTIs is limited. Critical questions regarding smell loss in COVID-19 remain unanswered, including the temporal profile of recovery, predictors of long-term olfactory dysfunction, and the relationship between smell function recovery with overall health recovery.

The COVID-19 pandemic offers a unique opportunity to understand the evolution of olfactory dysfunction for this particular viral infection. We used a self-reported survey to evaluate smell sensitivity and overall health recovery. The global objective of this study is to examine changes in smell recovery at the time of COVID-19 testing and the immediate weeks that follow, as well as compare changes in COVID+ viral illness to a cohort with COVID– viral illness.

Methods

An anonymous survey (UCSF Coronavirus Symptom Survey; see Suppl. Figure S1 in the online version of the article) was created and posted on social media from March 31, 2020, to April 22, 2020 (initial survey) to recruit participants with COVID-19–related general symptoms and test results. Follow up surveys were emailed to participants from April 14, 2020 to May 2, 2020. Responses with positive or negative COVID-19 test results were used for analysis. Within the survey, participants were queried about demographics, estimated date of COVID-19 test, test results, and estimated time to and presence of general health recovery (ie, feeling over 90% back to baseline health). Participants were also asked about smell sensitivity level (completely absent, noticeably decreased, or normal) within the 2 weeks prior to the COVID-19 test (T_0), as well as current smell level on the date of survey completion (T_1) and on a follow-up survey 2 weeks later (T_2) for a subset of participants who agreed to be contacted and completed a second survey. The Institutional Review Board at UCSF reviewed the study and granted exempt status (IRB 20-30530).

Smell Sensitivity Ratings

Smell sensitivity that was reported as completely absent was defined as anosmia, noticeably decreased as hyposmia, and normal as normosmia. Change in smell was analyzed from time of COVID-19 testing to time of the initial survey (T_0-T_1) and from the time of initial survey to the follow-up survey (T_1-T_2) by comparing rates of smell sensitivity categories between time points. Change from anosmia to hyposmia or normosmia was considered better, change from normosmia to hyposmia or anosmia was considered worse, and no change represented invariant smell ratings between time points. The participants were also grouped according to initial smell level at T_0, and changes in smell at the next two time points (T_1 and T_2) were evaluated for both COVID+ and COVID– participants.

Statistical Analysis

The survey was built using the Research Electronic Data Capture platform hosted at UCSF (REDCap Consortium, Vanderbilt University, Nashville, Tennessee), and data were analyzed using Microsoft Excel (Microsoft Corp) and the Statistical Package for the Social Sciences version 26 (SPSS, Inc). Demographic data were summarized using descriptive statistics and univariate analyses. The χ^2 analyses were used for contingency analyses of COVID+ and COVID– cohorts. Univariate analysis was used to determine significant differences in categories of smell change (better, worse, or no change) and recovery of general health in COVID+ vs COVID– participants at T_1 and T_2. Binary logistic regression analysis was performed to examine predictors for overall health recovery, including COVID-19 test result, smell sensitivity at the time of infection (T_0), and initial smell change from the time of infection to the initial survey (T_1-T_0). For all statistical analyses, a P value of $<.05$ was considered significant.

Results

Study Participants and Intertemporal Intervals

The initial survey was completed by 375 participants. Of these, 174 reported a positive COVID-19 test result and 201 reported a negative result. COVID-19 testing was limited in the United States and only available for symptomatic patients during the time of survey distribution. Both groups demonstrated URTI symptoms, with 184 (91.5%) of the COVID– cohort and 167 (96%) of the COVID+ group reporting at least 2 URTI symptoms at the time leading up to COVID-19 testing (T_0). The most common symptoms reported included fever, body ache, cough, and sore throat. Nasal congestion and/or rhinorrhea was reported in 59% of the COVID+ group and 49% of the COVID– group in the same initial time frame ($P > .05$). At the 2-week follow-up survey (T_2), 132 participants responded (62 COVID+ and 70 COVID–). The mean age of participants was similar between cohorts (**Table 1**). At the time of COVID test (T_0), 42% of the COVID+ cohort reported hyposmia or anosmia compared to 19% of the COVID– group (**Table 1**). The

Table 1. Demographic Information.[a]

Characteristic	COVID+	COVID–	*P* value
Age, mean (SD), y	38.4 (13)	37.8 (11)	.60
Sex, female	118 (66)	165 (80)	.003[b]
At time of infection			<.001[b]
Anosmia	41 (24)	7 (4)	
Hyposmia	32 (18)	31 (15)	
Normosmia	101 (58)	163 (81)	
General health recovery[c] at T_1	94 (53)	123 (59)	.241
Time to health recovery at T_1			.002[b]
<2 weeks	44 (47)	83 (67)	
2-4 weeks	50 (53)	40 (33)	

Abbreviations: COVID+, coronavirus disease 2019 positive; COVID–, coronavirus disease 2019 negative; T_1, the time of initial survey.
[a]Values are presented as number (%) unless otherwise indicated.
[b]$P < .05$ represents significance.
[c]General health recovery is return to >90% of baseline.

median time between T_0 and T_1 was 11 days with a range of 0 to 47 days. The median time between T_1 and T_2 was 14 days with a range of 13 to 20 days. The median time from T_0 to T_2 was 25 days with a range of 11 to 61 days. Based on the survey query about smell sensitivity in the 2 weeks prior to testing, the median time frame from symptoms to follow-up was estimated at 6 weeks. Ten (5.6%) of COVID+ and 4 (1.9%) of COVID– participants were hospitalized at some point during their illness.

Smell Loss and Recovery

Rates of normosmia at each time point differed significantly. At the time of COVID-19 testing (T_0), 58% of COVID+ participants reported normosmia compared to 81% of COVID– participants ($P < .001$). At the time of the initial survey (T_1), a stable percentage of the COVID+ (52%) and COVID– (86%) cohorts reported normosmia. By the time of the follow-up survey (T_2), normosmia increased to 74% for the COVID+ cohort compared to 94% of the COVID– cohort ($P < .005$). Rates of normosmia were lower for the COVID+ cohort at all 3 points ($P < .01$; **Table 2**).

Temporal dynamics of smell sensitivity at the time intervals between COVID test and initial survey (T_0-T_1) and initial survey to follow-up survey (T_1-T_2) for each participant were graded categorically as better, worse, or no change (**Table 3**). At the T_0 to T_1 time interval, 26% were better and 25% were worse in the COVID+ cohort compared to 11% better and 6% worse in the COVID– cohort. Between T_1 and T_2, 39% of COVID+ and 20% of COVID– participants noted better smell (**Table 3**). The distribution of smell sensitivity change (better or worse vs no change) at each time interval was different between the COVID+ and COVID– cohorts, with a larger proportion of the COVID+ cohort experiencing more dynamic changes in smell sensitivity over time ($P < .001$).

Temporal dynamics of smell sensitivity based on initial state (anosmia, hyposmia, normosmia) at the time of COVID-19 testing (T_0) revealed risk of normosmia degradation in the COVID+ cohort (**Figure 1**). (1) Normosmia at

Table 2. Temporal Evolution of Normal Smell in COVID+ and COVID– Cohorts.

			Normosmia, No. (%)			
Characteristic	COVID+, No.	COVID–, No.	COVID+	COVID–	χ^2	*P* value
T_0 (time of test)	174	201	101 (58)	163 (81)	23.8	<.001[a]
T_1 (time of survey)	166	195	85 (52)	168 (86)	52.2	<.001[a]
T_2 (time of follow-up)	57	65	42 (74)	61 (94)	9.4	.002[a]

Abbreviations: COVID+, coronavirus disease 2019 positive; COVID–, coronavirus disease 2019 negative; No., number.
[a]$P < .05$ represents significance.

Table 3. Smell Change Dynamics at 2 Time Intervals.[a]

	COVID+, No. (%)			COVID–, No. (%)			
Time interval	Better	Same	Worse	Better	Same	Worse	*P* value
T_0-T_1	44 (26)	81 (49)	41 (25)	22 (11)	161 (83)	12 (6)	<.001[b]
T_1-T_2	22(39)	35 (61)	0 (0)	13 (20)	51 (79)	1 (1)	<.001[b]

Abbreviations: COVID+, coronavirus disease 2019 positive; COVID–, coronavirus disease 2019 negative; No., number.
[a]T_0-T_1: time interval from COVID-19 test to time of survey (n = 361). T_1-T_2: time interval from first survey to second survey (n = 125).
[b]$P < .05$ represents significance.

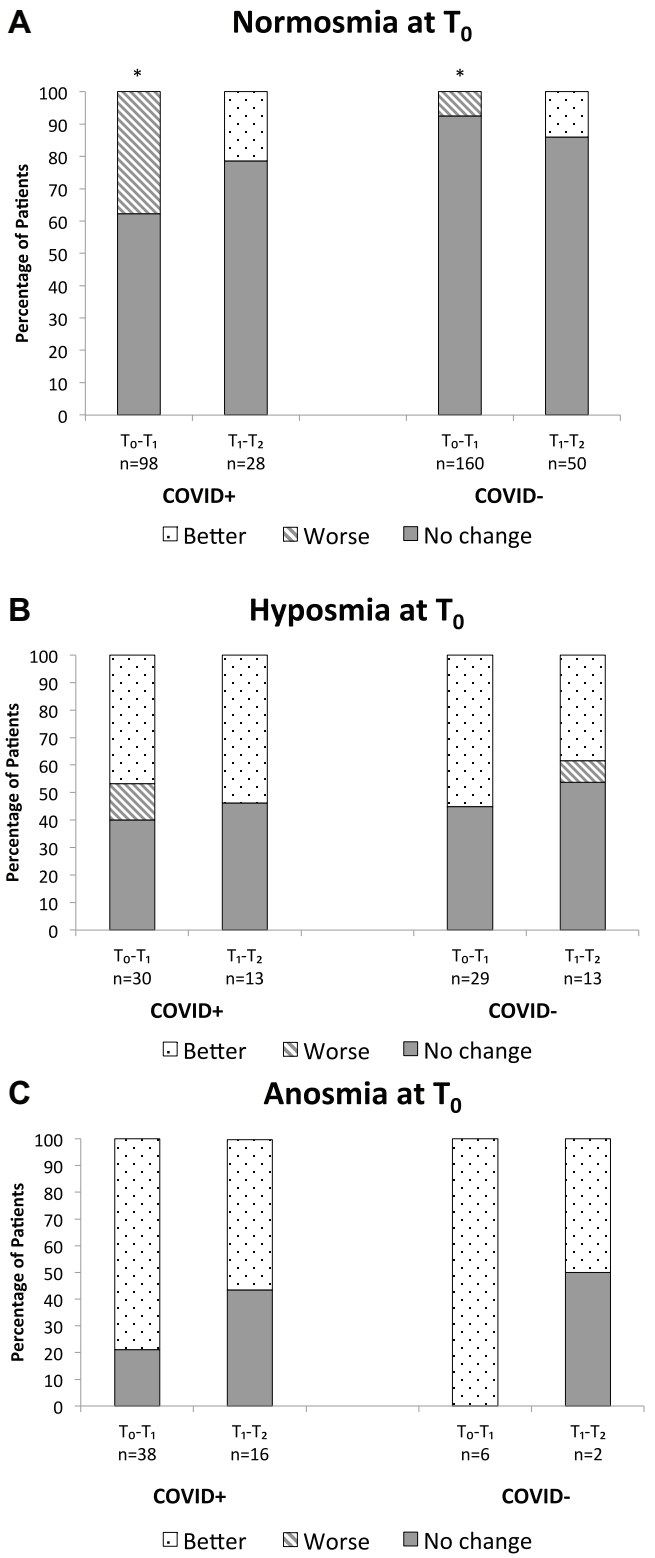

Figure 1. Change in smell from T_0 to T_1 and T_1 to T_2 for participants with initial normosmia (A), hyposmia (B), and anosmia (C). *$P < .05$ represents significance. COVID+, coronavirus disease 2019 positive; COVID–, coronavirus disease 2019 negative.

T_0: from T_0 to T_1, 38% of the COVID+ cohort reported worse smell compared to 8% of the COVID– cohort ($P < .001$). From T_1 to T_2, 21% of the COVID+ cohort reported better smell compared to 14% of the COVID– cohort ($P > .05$) (**Figure 1A**). (2) Hyposmia at T_0: from T_0 to T_1, 47% reported better smell and 13% reported worse smell in the COVID+ cohort, while 55% reported better smell in the COVID– cohort ($P > .05$). From T_1 to T_2, 54% reported better smell in the COVID+ cohort, while 38% reported better smell and 8% reported worse smell in the COVID– cohort ($P > .05$) (**Figure 1B**). (3) Anosmia at T_0: from T_0 to T_1, 79% of the COVID+ cohort reported better smell compared to 100% of the COVID– cohort ($P > .05$). From T_1 to T_2, data were not compared due to inadequate sample sizes (**Figure 1C**). Normosmia of the COVID+ cohort at the time of COVID-19 testing (T_0) was the sole statistically significant factor of temporally dependent dynamic change in smell sensitivity.

General Health Recovery

Time to general health recovery was delayed in the COVID+ cohort. At the time of the initial survey (T_1), 53% of the COVID+ and 59% of the COVID– cohorts reported overall general health recovery to >90% of baseline. Of these, 47% of the COVID+ cohort reported recovery within 2 weeks, compared to 67% of the COVID– cohort ($P < .05$; **Table 1**). On univariate analysis, initial smell level (anosmia vs hyposmia vs normosmia) was associated with general health recovery at T_1 ($\chi^2(2, N = 363) = 6.792$, $P = .034$), with a higher proportion of those who reported health recovery also reporting normosmia at T_0.

Initial state of normosmia and better smell sensitivity in the interval from T_0 to T_1 were associated with health recovery. Using multivariate analysis with logistic regression, anosmia or hyposmia at T_0 was associated with the lack of general health recovery at T_1, and better smell from T_0 to T_1 was positively associated with health recovery. COVID-19 test result and worse smell sensitivity were not associated with general health recovery (**Table 4**). Based on this analysis, an individual with improved smell from T_0 to T_1 was 10.9 times more likely to report general health recovery at T_1 relative to an individual with no smell change ($P < .001$). Inverted odds ratios demonstrated that if an individual reported anosmia or hyposmia at the time of testing at T_0, they were 10 times less likely to have general health recovery at T_1 relative to a participant with normosmia ($P < .002$).

Discussion

This manuscript advances the understanding of COVID+ infection in 3 ways. First, while olfactory loss was common to both COVID+ and COVID– infections, COVID+ smell function evolution was found to be more dynamic in the initial weeks, principally due to delayed degradation of normosmia at the time of initial infection. Second, anosmia at the time of initial infection was associated with slower general health recovery. Third, recovery to better smell sensitivity from T_0 to T_1 was associated with earlier overall health recovery.

Changes in smell sensitivity evolved more dynamically in the COVID+ cohort. Half of the COVID+ cohort

Table 4. Predictors for General Health Recovery to Baseline at T_1.[a]

Predictor	B	Wald	*P* value	Odds ratio (95% CI)
COVID-19 result	–0.1	0.16	.693	
Smell level at T_0			<.001[b]	
Anosmia	–2.03	10.0	.002[b]	0.1 (0.4-0.5)
Hyposmia	–2.36	20.7	<.001[b]	0.1 (0.03-0.3)
Smell change T_0-T_1			<.001[b]	
Better	2.39	17.7	<.001[b]	10.9 (3.6-33.3)
Worse	–0.59	3.0	.085	0.6 (0.3-1.1)

Abbreviation: COVID-19, coronavirus disease 2019.
[a]T_0: time of COVID-19 test. T_0-T_1: time interval from COVID-19 test to time of survey.
[b]$P < .05$ represents significance.

reported smell change between the time of COVID-19 testing and initial survey completion (approximately 11 days), in which one-fourth was worse and one-fourth was better with regard to olfactory sensitivity. Notably, within the COVID+ cohort who reported normal smell at the time of testing, 38% experienced worse smell sensitivity by the time of the survey. In contrast, very few COVID– participants reported worse smell within the same time frame. Furthermore, the rate of normosmia in the COVID+ cohort trailed the rate of normosmia in the COVID– cohort by 15% to 20% at both the time of COVID testing and the follow-up survey, although it is unknown whether this gap will close with longer follow-up or remain as a permanent sequela of COVID-19 infection. Consequently, the higher rate of dynamic changes in smell sensitivity and persistent olfactory dysfunction in COVID-19 highlights potential differences in the mechanism of virally mediated olfactory dysfunction between COVID-19 and non–COVID-19 infection.

COVID-19 olfactory dysfunction may occur without nasal symptoms, such as nasal obstruction[13,17] experienced during the common cold. This may be a differentiating feature of COVID-19 infection, as impaired olfaction and decreased nasal patency from mucosal edema are correlated[18,19] in other viral-mediated infections. COVID-19 olfactory dysfunction may be a consequence of direct insult to the olfactory epithelial cells, which has been posited as an etiology of longer-term PVOD.[9] It is known that SARS-CoV-2 viral entry into target cells depends on the viral spike protein. This protein binds with angiotensin-converting enzyme 2 (ACE2) and is primed by TMPRSS2 protease activity. Both ACE2 and TMPRSS2 are expressed in nasal epithelium and implicated in the transmission and infection of COVID-19.[20-22] Although ACE2 is not found on olfactory neurons, it is expressed on supporting cells and basal cells.[23]

Olfactory loss in COVID-19 infection has been reported to recover within weeks, which contradicts theories on olfactory neurosensory cell damage and PVOD typically associated with prolonged recovery on the order of months to years.[7] Boscolo-Rizzo et al[24] found that in 113 mildly symptomatic COVID+ patients with sudden altered smell or taste, 89% reported resolution or improvement in smell and taste 4 weeks later. Similarly, among 488 patients interviewed in Korea with sudden anosmia or ageusia, most recovered from these symptoms within 3 weeks.[25] In contrast, a study using objective olfactory testing in 72 COVID+ patients with sudden chemosensory loss found 37% had persistent anosmia or hyposmia after 5 weeks[26] and limited odor threshold detection compared to odorant identification, suggesting potential peripheral neurosensory damage.[26] At the present time, the exact mechanism of injury associated with olfactory loss in COVID-19 and the prevalence of PVOD in COVID-19 are unknown and under active investigation.

The relationship between olfactory dysfunction and general health recovery was elaborated by examining initial smell sensitivity (anosmia, hyposmia, normosmia) and its change from T_0 to T_1. On univariate analysis, initial smell level was associated with the presence of overall health recovery, with a higher proportion of those with initial normal smell reporting health recovery by the time of the survey. On multivariate analysis, improvement in smell from T_0 to T_1 was found to be an independent predictor for general health recovery when controlling for COVID-19 test result and initial smell sensitivity. Normosmia at T_0 was associated with general health recovery; hyposmia and anosmia were associated with lack of health recovery within the first few weeks of infection. These findings corroborate key findings of the Yan et al[27] study, in which 74% of COVID+ patients with olfactory loss demonstrated both improvement in olfaction and improvement in other COVID-19 symptoms, and patients who did not experience improved olfaction also did not experience improvement in associated COVID-19 symptoms.

Findings from this study have patient care implications. Patients with COVID-19 infection should be counseled that olfactory loss may fluctuate in the initial weeks. Smell sensitivity may worsen during a COVID-19 infection even if smell sensitivity is initially normal. The rate of PVOD beyond the first 4 to 6 weeks after infection is approximately 25%. General health recovery is associated with normosmia and improvement of smell sensitivity.

The primary limitations of this study relate to self-reported symptoms and recall bias. Data from self-reported dates for testing and recall of symptoms were used for analysis. Studies have demonstrated only moderate accuracy on the order of 79% for anosmia and 65% for normosmia with self-reported smell function levels limiting interpretation of the survey data.[28] Other sources of limitations are accuracy and variations of COVID-19 testing. Last, participants who completed the survey were mostly outpatients who did not require hospitalization and had Internet and social media access, thus limiting generalizability to all patients with COVID-19.

Larger prospective, longitudinal studies that include objective testing over an extended time period are needed to replicate and expand findings of this cross-sectional study. Future studies may focus on predictors for recovery of COVID-19 olfactory loss, the relationship between overall health recovery from COVID-19 infection and olfactory loss severity with its evolution toward normosmia, and identification of risk factors for patients more likely to suffer from COVID-19–associated PVOD.

Conclusion

In COVID+ and COVID– outpatient cohorts, the COVID+ cohort showed more dynamic change in smell sensitivity and higher rate of persistent olfactory dysfunction in the initial weeks after viral-mediated infection. Initial normosmia at the time COVID-19 infection may decline before recovery. Overall health recovery after viral illness was associated with improvement in smell sensitivity and the absence of initial anosmia or hyposmia.

Author Contributions

Patricia A. Loftus, data acquisition, data interpretation and analysis, manuscript writing; **Lauren T. Roland**, data acquisition, data interpretation and analysis, manuscript writing; **Jose G. Gurrola II**, study concept and design, data acquisition and interpretation and analysis; **Steven W. Cheung**, study concept and design, data interpretation and analysis, manuscript writing; **Jolie L. Chang**, study concept and design, data acquisition, data interpretation and analysis, manuscript writing.

Disclosures

Competing interests: Steven W. Cheung is a consultant to ProLynx LLC. Lauren T. Roland is a consultant to Tissium.

Sponsorships: None.

Funding source: None.

Supplemental Material

Additional supporting information is available at http://journals.sagepub.com/doi/suppl/10.1177/2473974X20978133

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